

# *Research Progress in the Treatment of Premature Ovarian Failure with Traditional Chinese Medicine*

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**Abstract:** Premature ovarian failure(POF) is defined as ovarian failure due to depletion of follicles within the ovary or iatrogenic injury before the age of 40 years. In recent years, POF tends to be younger and presents a high incidence, if not treated in time, it can cause infertility, postmenopausal osteoporosis, and other complications, seriously affecting the quality of life of patients. Many doctors have achieved good results in the treatment of POF with traditional Chinese medicine(TCM). This paper introduces the latest research progress of Chinese medicine in the treatment of POF, in order to find the mechanism and method of Chinese medicine in the treatment of POF.

## 1. Introduction

Premature ovarian failure (POF) refers to the premature and complete loss of ovarian function. POF refers to the onset of amenorrhea and high follicle stimulating hormone(FSH>40U/L), low estrogen levels and other endocrine abnormalities and perimenopausal symptoms, in women before the age of 40, which are the final stage of premature ovarian insufficiency (POI). There is no name of this disease in ancient Chinese medicine books, According to the clinical manifestations, this disease is classified as "blood dry", "amenorrhea", "infertility" and other categories. With the development of Chinese medicine in recent years, it has been proved that TCM syndrome differentiation is effective in treating POF from the perspectives of clinical observation, animal experiments, and network pharmacological research. Based on this, this paper summarizes the literature on TCM treatment of POF by various doctors in recent years, in order to provide ideas for the clinical diagnosis and treatment of POF.

## 2. Pathogenesis of POF

### 2.1. Mechanism of Western Medicine

The common causes of POF are mainly genetic, immune, iatrogenic, and other factors. Genetic factors account for 20%-25%, mainly including chromosomal abnormalities and gene variation 0. Immune factors are mainly due to autoimmune dysfunction resulting in ovarian function

impairment. Studies have found that 10%-30% of POF patients suffer from autoimmune diseases [2], such as Hashimoto's thyroiditis, Edison's disease, and systemic lupus erythematosus, which are closely related to POF. Surgery, chemotherapy, and radiotherapy belong to iatrogenic factors, Among the POF caused by iatrogenic factors, 64% occurred after ovarian surgery (except bilateral oophorectomy) [3], because surgery can lead to ovarian tissue defect or local inflammation, thus affecting the ovarian blood supply and leading to POF. Chemotherapy drugs such as cyclophosphamide can induce oocyte apoptosis or destroy the function of granulosa cells to induce POF (Table 1). In addition to the above three factors, other factors such as environmental factors, poor diet, and lifestyle can affect ovarian function.

Table 1: Western medicine pathogenesis of POF

Western medicine pathogenesis of POF	Contains content	proportion
Genetic factors	Chromosomal abnormalities and gene variation	20%-25%
Immune factors	autoimmune diseases	10%-30%
iatrogenic factors	ovarian surgery	64%

## 2.2. Mechanism of TCM

The occurrence of POF is mainly related to the deficiency of kidney essence and the dysfunction of viscera. The production of menstruation is dominated by the kidney, "Huangdi Neijing" said: "The woman is seven years old, kidney qi sheng... 27 and the day decays to... Month to present ", kidney with congenital , hidden essence, main reproduction, congenital lack of endowment or acquired room labor, prolific injury kidney, resulting in kidney deficiency, visible menstrual suspension, month water cut off prematurely. According to the Women's Rule in Jingyue, "Blood is the essence of the water valley... Biochemical in the spleen, president in the heart, hidden in the liver, announced in the lung, and discharge in the kidney." Heart hidden God, the main blood, women worry in the heart, heart gas can not pass, resulting in cellular impassability, chong Ren disorder, amenorrhea, infertility, etc. Spleen is the basis of the acquired, diet is not good, excessive thinking leads to spleen deficiency and little blood Qi, and blood biochemistry is passive, then there is no water. The liver contains blood, women's menstrual cycle, pregnancy, childbirth, and milk are all used with blood, emotional depression and anger first hurt the liver, liver qi loss in the drainage, qi and blood disorders, Chong Ren loss can be seen amenorrhea, infertility. The regulating effect of the lung is less, but the lung is the mother of the kidney, and the mother injury can reach the son. Human body is a whole, one viscera injury is five viscera injury, so the treatment of POF should be based on the kidney, five viscera in tune.

## 3. TCM Therapy

### 3.1. Chinese Medicine

Jinkui Wenjing Decoction is mainly used for soothing the liver and strengthening the spleen, tonifying the blood and regulating the menstruation, and regulating the chong and Ren meridians. Zhang et al.[4] found that the total effective rate of the treatment group (97.9 %) was significantly higher than that of the control group (85.4 %). Jinkui Wenjing Decoction can adjust the level of serum sex hormone, improve the secretion of serum estrogen in POF patients, and improve the therapeutic effect. Yulinzhu was involved in treating renal qi deficiency infertility. He et al.[5] found that high-dose Yulinzhu could improve the ovarian function of POF model rats induced by cyclophosphamide, increase the number of mature follicles and reduce follicular atresia, which

might be achieved by activating SIRT1/FoxO1 pathway, inhibiting oxidative stress and autophagy, and thus improving the ovarian function of POF rats. As a classic kidney tonifying prescription, modern studies have found that Zuogui Pill has estrogen-like effects. Zhao et al.[6] found that Zuogui Pill can increase the expression of follicular estrogen receptor (FSHR) and estrogen receptor (ER) in hypothalamus, pituitary and ovarian tissues, promoting the growth and development of follicles at all levels, and high-dose group has a significant effect. Liu et al.[7] found that Zhuhuang Decoction can effectively improve the clinical symptoms of POF patients, regulate the levels of sex hormones such as FSH and Anti-Mullerian Hormone(AMH), and improve ovarian function, with high safety. Erzhi Pill reinforced liver and kidney. Chen et al.[8] found that the level of estradiol (E2), ovarian index, uterine index, and the relative expression of ER $\beta$  of rats in the medium and high dose groups of Erzhi pills were significantly increased, suggesting that Erzhi Pill can stimulate the growth and differentiation of follicles and maturation of follicles followed by ovulation by regulating the level of serum sex hormones, to achieve the purpose of treatment. Studies have found that the age of amenorrhea is positively correlated with the detection rate of antinuclear antibody (ANA) in POF patients, while low female pregnancy rate is closely correlated with anti-ovarian antibody (AOA). Dong et al.[9] found that ANA and AOA in POF patients decreased significantly after treatment with Bushen Huoxue Decoction, Bushen Huoxue Decoction may be through downregulating the concentration of immune antibodies, regulating the ANA-ACA-AOA pathway, and delaying the ovarian granule to achieve the purpose of relieving POF. Zhou et al.[10] found that compared with the control group, the contents of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and  $\gamma$ -interferon (IFN- $\gamma$ ) in the serum of POF model rats in Erxian Decoction treatment group were significantly decreased, the expressions of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in ovarian tissue were significantly increased, suggesting that Erxian Decoction could enhance the ovarian reserve function by regulating the level of sex hormones and promoting the expression of related growth factors, in a certain dose-dependent manner (Figure 1).

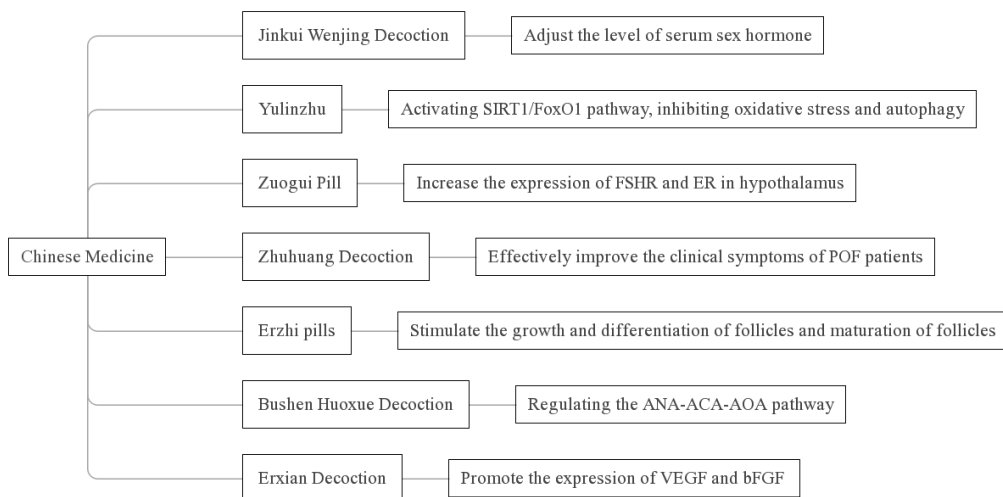


Figure 1: Chinese Medicine.

### 3.2. TCM Monomer

Resveratrol is a polyphenolic natural phytoantitoxin present in a variety of plants. It has a variety of pharmacological effects such as anti-inflammatory, anti-oxidation, cytoprotection, and anti-apoptosis [11]. Xiu et al.[12] Found that after resveratrol intervention, the expression of  $\beta$ -caterin positive protein in ovarian tissue of POF model mice increased in a

concentration-dependent manner, the expression of Mvh, Oct4, SOD2, Nrf2 and Bcl-2 proteins is also increased. Resveratrol has a protective effect on POF mice, and its mechanism may be related to the activation of Wnt/ $\beta$ -catenin pathway to promote the recovery of ovarian function. Icaritin has the function of regulating the hypothalamic-pituitary-ovarian axis and is now widely used in the treatment of irregular menstruation, amenorrhea and other diseases [13]. Wang et al.[14] Found that icaritin can reduce serum FSH and LH levels, increase serum E2 content, promote follicular development, and enhance ovarian reserve function. Thus, it has a therapeutic effect on D-galactose (D-gal)-induced POF model mice. Curcumin is extracted from the traditional Chinese medicine turmeric. As an antioxidant, curcumin can promote follicular formation and reduce cell apoptosis [15]. Yan et al.[16] Found that curcumin can increase ovarian AMH expression and promote follicular development, this may be through Nrf2/HO-1 and PI3K/Akt signaling pathways to reduce D-gal -induced oxidative stress, apoptosis, and ovarian damage. Liang et al.[17] found that after the treatment with the extract of Shiyao *Angelica sinensis*, the level of E2 in POF model mice increased, the level of FSH and luteinizing hormone (LH) decreased, and the mRNA and protein expressions of Rictor and mTORC2 increased. The effect was most obvious in the high-dose group, and Shiyao *Angelica sinensis* extract could improve the disorder of sex hormone in POF rats, promote follicle maturation, and the mechanism may be related to the activation of Rictor/mTORC2 signaling pathway. Liu et al.[18] Found that ginsenoside Rg1 could increase the expression of superoxide dismutase (SOD) and catalase (CAT) in POF model mice to regulate the ovarian state, reduce ovarian oxidative damage, delay ovarian aging, and increase the expression of ovarian aging regulatory factor SIRT1. It is suggested that ginsenosides can regulate SIRT1 expression in ovarian tissue to delay POF (Figure 2).

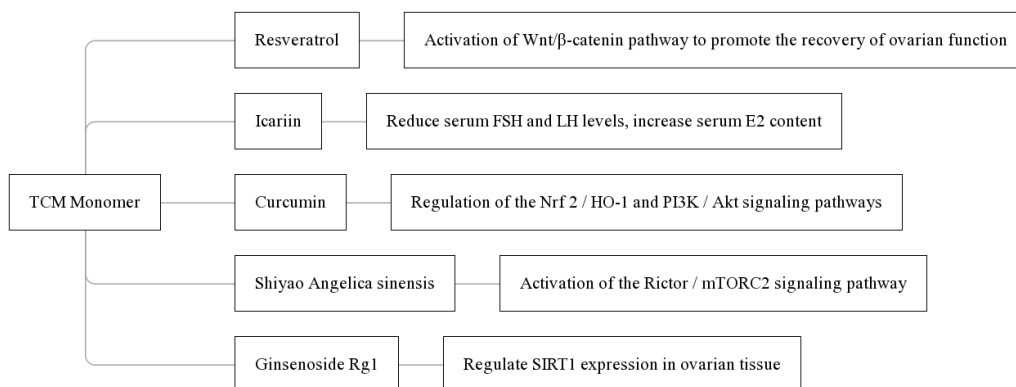


Figure 2: TCM Monomer.

### 3.3. Proprietary Chinese Medicine

Han et al.[19] found that gavage of Jiawei Bazhen Yimu Capsule could increase the level of E2 in rats, increase the positive expressions of ESR1, CYP3A4 and CYP19A1 related to estrogen signaling pathway in uterine tissue, play a hormone-like role, regulate hormone imbalance and improve uterine state to achieve therapeutic effects. Wei et al.[20] found that Guizhi Fuling Capsule could significantly improve the level of sex hormone in POF rats, and the medium dose had the best effect, Guizhi Fuling Capsule could inhibit the phosphorylation of p-38 MAPK and the activation of downstream Fas/FasL signaling pathway, thus reducing the apoptosis of ovarian cells. After treatment with Kuntai capsule, Dai et al.[21] found that the number of ovarian follicles in rats increased, the disturbance of the estrous cycle, and ovarian function was improved, and serum sex hormone levels gradually returned to normal, the mechanism may be related to the upregulation of

Fas protein and mRNA expression and the down-regulation of FasL protein and mRNA expression. Pan et al.[22] and Zhou et al.[23] found that Kuntai capsules and Apocynum venetum granules could downregulate the expression of Bax protein while increase the expression of Bcl-2 protein in ovarian tissue, increase the ratio of Bcl-2/Bax, promote the ovarian growth of mice with immune POF, and inhibit the excessive apoptosis of follicles, Improve the ovarian function of rats to achieve the purpose of POF treatment. Huang et al.[24] suggested that Xianziyizhen capsule, a Chinese medicine for tonifying the kidney and filling essence, could improve the quality of follicles and ovarian function, increase the contents of follicles at all levels and reduce the number of atretic follicles, and its mechanism might be related to the enhancement of PI3K/AKT pathway activity and cell proliferation in ovarian cells(Figure 3) .

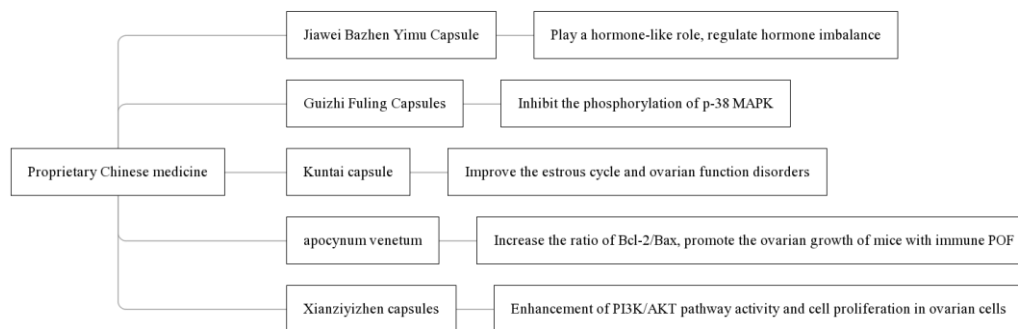


Figure 3: Proprietary Chinese medicine.

### 3.4. Herb Pair

Herb pair refers to a prescription composed of two relatively fixed herbs in clinical practice, which has the effect of "multi-component, multi-target and multipathway". Wang et al.[25] found that a pair of herbs of Coastal Glehnia Root-Polygonatum Odoratum could improve the clinical symptoms of POF, increase the number of follicles at all levels, promote the growth of follicles, upregulate the level of PI3K and Akt, inhibit the expression of PTEN and NF- $\kappa$ B, inhibit the apoptosis of ovarian granulosa cells and improve POF by interfering with inflammation and oxidative stress. Shang et al.[26] found that a pair of herbs of Ligustrum lucidum Dipsacus could improve the ovarian index and uterine index of POF model rats and regulate serum hormone levels, especially in the improvement of serum E2 levels, indicating that Ligustrum lucidum-Dipsacus has plant-like estrogen activity, which can effectively regulate the level of related estrogen in the body and prevent the occurrence of POF. Li et al.[27] found that the key targets of Cuscutae Semen-Lycii Fructus herb pair were AKT1, TP53, CASP3, etc. which may improve the growth and development of follicles, proliferation and differentiation of granulosa cells, and growth of oocytes by regulating the PI3K/Akt metabolic pathway, thus playing a therapeutic role. Hu et al.[28] found that the main active components of curculigo orchioides epimedium in the treatment of decreased ovarian reserve function may be quercetin, luteolin,  $\beta$ -sitosterol, and the main targets may be AKT1, IL-6, TP53, VEGFA, etc. The possible pathways involved include AGE-RAGE signaling pathway, IL-17 signaling pathway, PI3K-AKT signaling pathway, cell apoptosis, HIF-1 signaling pathway, etc (Figure 4).

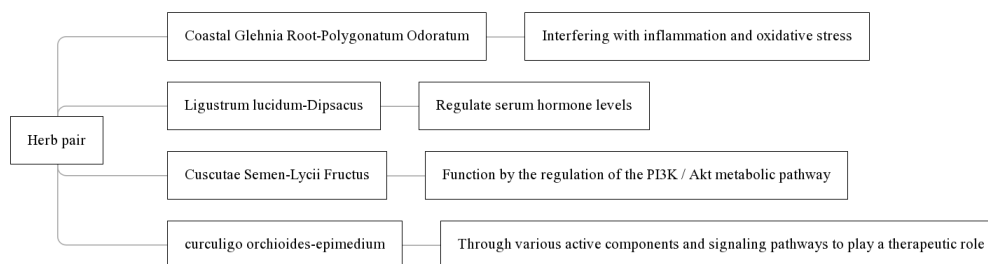


Figure 4 : Herb pair.

## 4. Summary

Hormone replacement therapy, stem cell therapy, mesenchymal stem cell therapy, and ovarian transplantation are commonly used in Western medicine to treat POF. However, these methods have disadvantages such as high price, obvious adverse reactions, and increased risk of endometrial cancer and breast cancer. In recent years, the incidence of POF tends to be younger and higher, which will lead to infertility, perimenopausal symptoms, and seriously affect women's physical and mental health. Therefore, the prevention and treatment of POF is particularly important, and people urgently seek safe and effective treatment plans. With the development of Chinese medicine, TCM is often used to treat POF. This paper integrates the literatures on the treatment of POF by domestic and foreign doctors in recent years to provide ideas for the clinical diagnosis and treatment of POF by doctors.

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